African J. Biol. Sci., 16 (1): 207-231 (2020)
ISSN 1687-4870 e- ISSN 2314-5501 (online)
www.ajbs.journals.ekb.eg E.mail: aasdjournal@yahoo.com

Urtica dioica improves brain dysfunctions in propionic acid autistic like rat model through brain monoamines and mitochondrial energy

Elham H.A. Ali [1*], Mohamed K. Hassan[2], Osama A. Abbas[2], Heba E. Elmalahy[2] and Ali H. Abu Almaaty[2]

1- Zoology Department, Faculty of Women for Arts, Science and Education, Ain Shams University, Egypt

2- Zoology Department, Faculty of Science, Port Said University, Egypt

* Corresponding author Email: elham.ali@women.asu.edu.eg , elhamhassan2006@yahoo.com

Received: March 21, 2020; Accepted: April 30, 2020; Available Online December 27, 2020

ABSTRACT

The present study was designed to investigate the effect of *Urtica dioica* plant parts "leaves and roots" separately, known as stinging nettle, on propionic acid (PPA) induced autistic like rat model on the behavior, monoamines and bioenergetics changes in rats compared with the synthetic drug risperidone. Sixty male albino rats were divided into 5 equal groups (n=12) and treated for 17 days as follows: 1- control {received (0.1M, PBS as 1ml/kg b.wt ip) and (0.5/100 w/v as 5ml/kg b.wt p.o) of carboxy methyl cellulose (CMC), 2- PPA received (250 mg/kg as 1 ml/kg b.wt; i.p) + CMC p.o. as control, group, 3- PPA+ RISP (1mg/kg b. wt, p.o), 4- PPA+ nettle leaves (NL, 50mg/kg b. wt, p.o) and 5- PPA+ nettle roots (NR, 50mg/kg b. wt, p.o). The three-box chamber and Y maze tests were performed from 15th to the 17th day. In the 18th day, rats were sacrificed and homogenates of cortical, hippocampal and midbrain tissues were used for the estimation of dopamine (DA), norepinephrine (NE) and serotonin (5-HT) contents along with the bioenergetics (ATP, ADP and AMP). The results showed that NR extract could attenuate behavior deficits together with the improvement of the monoaminergic system and bioenenrgetics. In contrast, NL extracts had a poor effect on behavioral improvement, monoamines levels and the bioenergetics. Therefore, it may be concluded that NR extract had a protective effect due to its impact on the behavioral, monoaminergic and bioenergetics systems.

Keywords: *Urtica dioica* , stinging nettle , propionic acid, risperidone , autistic disorder, mental retardation, behavioral improvement.

INTRODUCTION

Autism is a syndrome which is characterized by deficit in social interaction and repetitive behavior pattern caused by improper neuro-developmental process appear on children before 3 years of age. It is a spectrum multifaceted disorder. The prevalence of autism changes rapidly from 1 out of 10,000 children in the 1980's. But, in 2008, pervasiveness is 1 in every 88 children to the current statics 1 in 59 in 2018. The huge increase may be due to the border of criteria expanded in diagnosis of autism spectrum disorder (ASD) that is mainly neurobehavioral and also associated with much medical co-morbidity (Bjørklund *et al*., 2020).

Propionic acid (PPA), one of the main short chain fatty acids, plays particular role in the development, metabolism and immunity in health, but also in some inherited and acquired diseases, including those which affect brain function and behavior (Aguirre and Venema, 2017). High levels of PPA are accompanied by developmental delay, oxidative stress and metabolic or immune

disturbances, which have some similarities with propionic acidemias and autism (Nankova *et al*., 2014).

The genus *Urtica* is a member to the family Urticaceae in the major group Angiosperms (flowering plants). *Uritica* compounds are very important in medicine and pharmacology. For example, histamine has beneficial effect on the complex physiology of brain systems, affecting cognitive processes, including learning and memory (Blandina *et al*., 2004) most notably its inhibition of myeloid dendritic cells (Broer and Behnke, 2002), shows a protective impact against cerebral ischemia/reperfusion damage (Hornick *et al*., 2011), while modifying dopamine and serotonin concentration in the prefrontal cortex and hippocampus. *Urtica dioica* extract has been reported to improve spatial and associative memory dysfunction associated with chronic diabetes (Patel *et al*., 2015).

Risperidone acts on serotonin and dopamine and this makes it a choice to treat negative symptoms of schizophrenia and to reduce positive symptoms (Pajonk, 2004) and moderate autism behavior like quick mood change, self-injury, aggression toward others specially at low dose (Kirino, 2014).

The monoamine neurotransmitter including dopamine (DA), norepinephrine (NE), and serotonin (5-HT). Its main function is to keep brain normal development regulation movement, social communication, memory and general behavior (Choudhury *et al*., 2012). Based on these facts, neurotransmitters imbalance implicated in pathophysiology of autism (Chugani *et al*., 2001). NE major function is adapting to environmental change enhance flexibility and respond to emergent situation important in learning process (Sadacca *et al*., 2017). DA is inhibitory expiatory catecholamine and its main function is to regulate rewarding circuit that would be inhibited in autistic patient due to lack of communication in addition manage movement system (McNamara *et al.*, 2014). Serotonin is a signaling molecule cross the body that mainly play a role in cell development generally (Celada *et al*., 2013) and specially neurons including proliferation, differentiation, migration, apoptosis synaptogenesis, neuronal and glial development alternation in serotonin distribution is linked to neuro-developmental disorder like diagnosis of autism spectrum disorder, ASD (Muller *et al*., 2016).

ASD is a grouped of metabolic disorders with multiple contribution to mitochondria dysfunction (MD) (Siddiqui *et al.,* 2016) that were confirmed by a lot of researches and clinical investigations to individuals with ASD that considered MD a medical condition associated with it. Mitochondria is a powerhouse that provide cells with ATP. Especially, those that have a highly demand to energy like neurons (Zhu *et al*., 2012) contain many of it. Any disturbance in its function will affect directly the production of ATP. So measuring cellular bioenergetics (ATP, ADP, and AMP) can be a biomarker for mitochondrial disorders (Chacko *et al.,* 2014 & 2019).

The aim of this work is to investigate the beneficial effect of *Urtica dioica* plant parts (leaves and roots) separately on the behavior; monoamine system and energy carriers in the brain of autistic like rat model induced by propionic acid and compared the obtained results with the synthetic drug used for treatment of ASD, risperidone.

MATERIALS AND METHODS

Animals:

A total of 60 young male rats weighed about 45-60 g (approximately 21 days old) were obtained from the animal house of Faculty of Pharmacy Mansoura University. Animals were housed in the animal house of Faculty of Science, Port-Said University. Rats were distributed randomly in standard cages (n= 6 per cage) to prevent over-crowding. The animal

house maintained at 24°C and 50-60% relative humidity. A 12-hour dark/light cycle was maintained during the period. Rats had free access to food and water ad libitum. All experiments were performed according to the animal guidelines of Port-Said Faculty of Science and Ain Shams University.

Drugs:

Carboxy methylcellulose (CMC) was supplied as a white powder (Sigma Aldrich). Propionic acid was supplied as a solution (99.9% purity), purchased from Sigma (St. Louis, USA). The plant roots were supplied as herbal supplement capsules (500 mg/capsule), purchased from Swanson health product (USA). The plant leaves were supplied as herbal supplement capsules (200mg/capsule), purchased from Solgar, Inc, (NJ, U.S.A). Resperidone drug was supplied as tablets (4 mg), purchased from JANSSEN-CILAC.

Experimental design:

Sixty animals randomly divided into five groups (n=12), as follows:

1-Control group: received buffer phosphate saline 0.1 M as 1 ml/kg b.wt/day intraperitoneal and CMC (0.5 g /100 ml) as (5 ml/kg b.wt/day) by oral gavages injection daily through the experiment duration.

2- Propionic acid group: received PPA dissolved in 0.1 M Phosphate Buffered Saline and injected intra-peritoneally as 250 mg/kg (0.26 M, 1ml/kg b.wt/day) + CMC (0.5 g /100 ml) as (5 ml /kg) by oral gavages injection (Choi *et al*., 2018).

3- Propionic acid + Risperidone drug group: received PPA at the same dose + Risperidone drug (1mg/kg b. wt/ day, as 5 ml /kg/ day po.) through the experiment duration.

4- Propionic acid + Nettle leaves extract group: received PPA with the same dose + Nettle leaves extract (50mg/kg) as (5ml /kg/day po.) by oral gavages daily through the experiment duration.

5- Propionic acid + Nettle roots extract group: received the same PPA dose + Nettle roots extract (50mg/kg) as (5ml /kg/ day po.) by oral gavages daily through the experiment duration.

Behavior analysis: the three box chamber and Y maze tests were performed in the days 15^{th},16^{th}, and 17^{th} after one hour at least from the time of the daily injection. All the investigated groups were treated for 17 days then decapitated in the 18^{th} day. The brain was removed on ice within 30seconds from the skull (Yashpal and Henry, 1984).

Three box-chamber sociability test:

The social test was performed in a three chambered apparatus as described by Nadler (2004); Ali and Elgholy (2013). The maze was obtained from Zoology Department of Women Faculty of Arts, Science and Education- Ain Shams University. It is a Plexiglass box with partitions separating the box into three chambers with dimensions (length/ width/height in cm) 60/40/30. The openings between compartments allowed free exploration to the different chambers. Time spent in each chamber, as well as the time spent exploring the stranger rat or an object in the chamber, was analyzed. The object was an empty identical cage used to enclose the stranger rat. Chambers were cleaned with 70% ethanol and water between tests. Animals used as "strangers" were males with the same age"21 days" and no previous contact with the test rats. For the sociability test, rats allowed expending 10 min in the central chamber, and then the stranger rat was introduced into one of the side chambers. The experiment was performed for up to 10 min, with the stranger rat and an object on each side. The three chambered apparatus was center don to a lab bench to minimize light gradients in temperature, sound and

other environmental conditions that could produce a side preference. The number of entries was recorded when the four limbs of the rat passed the gate of the chamber.

Y maze: comprises of a capital Y-shape, with three arms marked A, B, and C. The point between the arms is 120^{o}; every division of the maze is 40 X 15 X 30 cm, long X wide X high individually (Roghani *et al.*, 2006). The floor and sides of each arm are made of wood. The maze utilized to evaluate spontaneous alternation. Each rodent was placed in one of the arms (arm A) confronting the focal point of the maze and allowed to move freely among the three segments for 5 min. The absolute number of arm passages was recorded by an advanced camera to assess the locomotion. A passage was possibly recorded if each of the four appendages were set into the arm. The all out number of arms entered gives a sign of locomotion activity, and the request for arms entered gives a proportion of spontaneous alternation and in this way assess working memory and stereotypic conduct. The maximum spontaneous alternations is determined as the spontaneous alternation X 5 less two, the correct alternation is determined as the progressive passages into the diverse three arms on covering triplet sets (i.e., ABC, CBA, BAC), the percentage alternation is calculated as {(actual alternations/maximum alternations) x 100}, and the percentage of correct alternation is calculated as {(correct alternation/maximum alternations) x 100}. The maze was cleaned with 70% alcohol and allowed to dry between sessions (Roghani *et al*., 2006; Hegazy *et al*., 2016).

Biochemical analysis:

Each brain of 6 different individuals per group was kept frozen for the biochemical investigation. The brain tissues were extracted on the ice at room temperature and dissected to obtain the frontal cortex, midbrain and the hippocampus from each brain. The obtained tissues were grinded well by using the manual grinder at potassium phosphate buffer (PBS; 7.2 PH) as 10% weight/volume of tissue homogenate buffer, i.e. (0.7 mg brain tissue in 7 ml buffer). Then spine at 2000Xg for 2 min to partially clarify and separate the aqueous layer from supernatant then kept in -20^{o}C for the biochemical investigations.

Estimation of the brain catecholamines (cortex, midbrain and hippocampus):

The Agilent HPLC system used with Rheodyne injector 20µl loop and an ultraviolet (UV) variable wavelength detector was used for monoamine assays where the samples were injected directly into an AQUA column C18, purchased from Phenomenex, the USA under the following conditions: mobile phase 97/3 from 20Mm potassium phosphate, pH 3.0/ methanol, flow rate 1.5ml/min, UV 270 nm. NE, DA, and 5-HT were separated after 10 minutes. The obtained chromatogram identified each monoamine position and concentration from the sample as compared to that of the standard, and finally, the calculation of the content of each monoamine as µg per gram brain tissue was made according to Pagel *et al*. (2000).

Measurements of energy carrier's molecules:

The detection of AMP, ADP, and ATP by HPLC was done according to the method of Liu *et al.* (2006). Two hundred microliters of samples (supernatant of brain tissue) was added to 1ml of 70% methanol for deprotonization. The samples were centrifuged at 4500 rpm for 5 min and used for HPLC analysis. Samples were eluted isocratically and analyzed on C-18 Spherclone column, mobile phase divided into A, B Where: A→ (0.04 M monobasic potassium phosphate, pH=5.5), B→ (0.5 M monobasic potassium phosphate, pH=5.5), A/B: 100 / 0 in 26 min A/B reach to 0 /100, within flow rate (1ml/min),

chromatographic determination was performed on Perkin – Elmer HPLC. The report and chromatograms were taken from data acquisition program purchased from Perkin–Elmer at wave length 254 nm and injection volume 20 µl.

Statistical analysis:

Values are means ± standard error of 6 animals for biochemical analysis and 12 animals for behavior tests. Analysis of variance (ANOVA) was performed using a Statistical Package for Social Science (SPSS, V.23, USA). Once a significant F value was obtained, post hoc LSD test was performed using the same program.

RESULTS

By estimating the cortex norepinephrine (COR-NE) values, it was noticed a high significant ($P < 0.001$) depletion in COR-NE contents of the PPA, PPA+RISP and PPA+NL treated groups as compared with the CON group. On the other hand, PPA+NR treated group exhibited a high significant ($P < 0.001$) increase in COR-NE contents in comparison with the PPA treated groups. Moreover, a significant ($P < 0.05$) decrease in hippocampus norepinephrine (H-NE) in PPA+RISP, PPA+NL, and PPA+NR treated groups in comparison with the CON group was observed. Also, the PPA+NR, PPA+NL groups showed a high significant ($P < 0.001$) reduction in the midbrain norepinephrine (Mb-NE) value when compared with the CON group. As well as, PPA, PPA+RISP treatment induced significant ($P < 0.01$) decrease in the Mb-NE contents when compared with the CON group as shown in Table (1).

The recorded values of COR-DA contents revealed that the PPA, and PPA+NL treated groups showed a high significant ($P < 0.001$) depletion as compared with the CON group. Also, PPA+NR group exhibited a significant ($P< 0.01$) decrease in COR-DA content as compared with the CON group (Table 1). While, the PPA+RISP treated group showed a high significant ($P< 0.001$) increase in the COR-DA values when compared to the PPA treated group. The PPA+NR treatment caused a significant ($P < 0.01$) increase in COR-DA as compared to the PPA treatment.

The result of measuring dopamine in the hippocampus indicated that the PPA+NR treated group has a high significant ($P < 0.001$) decrease when compared to the CON group. Moreover, the PPA+NL treated group exhibited a significant ($P < 0.01$) diminution in the value of H-DA when compared to the CON group. Also, the PPA treated group showed a significant ($P < 0.05$) decrease in the value of H-DA when compared to the CON group. In contrast, the PPA+RISP treatment induced a significant ($P < 0.05$) increase in H-DA values as compared to the PPA treatment. While, the PPA+NR treated group exhibited a significant ($P < 0.01$) depletion in the level of H-DA when compared to the PPA treated group. Data showed that the PPA, PPA+RISP, PPA+NL, and PPA+NR treated groups exhibited a high significant ($P < 0.001$) depletion in Mb-DA contents as compared to the CON group. While, PPA+NL treated group revealed a significant increase ($P < 0.01$) in Mb-DA contents as compared with the PPA group.

Data in Table (1) showed that the PPA and PPA+NL treatment induced a high significant ($P < 0.001$) reduction in the COR-5HT contents when compared with the CON group. Also, the PPA+RISP, and PPA+NR treatment caused a significant ($P< 0.05$) decrease in the COR-5HT contents when compared with the CON group. However, high significant ($P < 0.001$) elevations in COR-5HT contents were induced by PPA+NR, PPA+RISP treatment when compared with the PPA treatment. However, the PPA, PPA+RISP and PPA+NL treated groups showed a statistically but not significantly change in

the level of H-5HT when compared to the CON group. Moreover, no significant change was noticed in PPA+RISP or PPA+NL in the level of H-5HTin comparison with the PPA treated group. While, PPA+NR treated group displayed a significant ($P < 0.05$) depletion in the level of H-5HT when compared to the CON group. Also, it showed a significant decrease ($P < 0.01$) when compared to the PPA treated group. A high significant ($P < 0.001$) decrease in the Mb-5HT contents were observed in the PPA, PPA+RISP and PPA+NL treated groups when compared with the CON group. Also, there was a significant ($P < 0.05$) reduction in the PPA+NR group in the Mb-5HT contents as compared to the CON. A significant ($P < 0.05$) increase was shown in Mb-5HT contents in PPA+NR treated rats as compared to the propionic acid treated group.

Table (1) : Effect of different treatments by stinging nettle leaves (NL), roots (NR) and risperidone (RISP) drug on monoamine (norepinephrine (NE), Dopamine (DA), serotonin (5-HT)) contents (ug/g wet tissues) in the cortex, hippocampus and midbrain of rats induced by propionic acid (PPA).

	Groups	Cortex	Hippocampus	Midbrain
NE	CON	0.72±0.027	0.47±0.024	0.51±0.017
	PPA	0.52±0.021 a***	0.4±0.026	0.40±0.015 a**
	PPA+RISP	0.55±0.015 a***	0.38±0.023 a*	0.39±0.026 a**
	PPA+NL	0.47±0.02 a***c*	0.38±0.040 a*	0.37±0.017 a***
	PPA+NR	0.67±0.014 b***c***d***	0.37±0.009 a*	0.37±0.031 a***
DA	CON	1.7±0.044	1.1 ±0.048	1.3±0.048
	PPA	1.2±0.0395 a***	0.96±0.043 a*	0.78±0.034 a***
	PPA+RISP	1.6±0.052 b***	1.1 ±0.022b*	0.87±0.004 a***
	PPA+NL	1.1±0.034 a*** c***	0.92±0.025 a**c**	0.96±0.068 a***b**
	PPA+NR	1.4±0.079 a**b** d***	0.81±0.027	0.85±0.043 a***
5-HT	CON	0.75±0.019	0.43±0.027	0.54±0.034
	PPA	0.47±0.032 a***	0.44±0.029	0.37±0.027 a***
	PPA+RISP	0.68±0.025 a*b***	0.38±0.013	0.39±0.019 a***
	PPA+NL	0.47±0.018 a***c***	0.44±0.023	0.34±0.013 a***
	PPA+NR	0.66±0.029	0.34±0.028 a*b**d**	0.46±0.014

Values are means± SE of six rats, a=significant difference compared with control group(CON), b= significant difference compared with propionic acid group (PPA), c=significant difference compared with propionic acid + Risperidone treatment group(PPA+RISP), d= significant difference compared with propionic acid + nettle leaves treatment group(PPA+NL), propionic acid +nettle roots (PPA+NR), *Significant level of probability ($P<0.05$), ** Significant level of probability ($P < 0.01$), *** Significant level of probability ($P <0.001$), Non-significance ($P \geq 0.05$) .

It was obvious from data in Table (2) that the PPA, PPA+RISP, PPA+NL and PPA+NR treatments induced a great significant depletion ($P < 0.001$) in the concentration of COR-ATP when compared to the control group. Moreover, PPA+RISP and PPA+NR groups exhibited a significant increase ($P < 0.01$) in the

COR-ATP content in comparison with the PPA treated group. In contrast, the PPA+NL treated group induced a significant depletion ($P < 0.05$) in the level of COR-ATP in comparison with the PPA group. The data obtained from hippocampus revealed that there wasn't any significant detected in H-ATP between PPA administrated group and the control. Also, there wasn't significant change in the PPA+RISP, and PPA+NL group when compared with control or PPA group. But a high significant decrease ($P < 0.001$) was observed in the PPA+NR when compared to the control and PPA treated groups. Moreover, all the treated groups showed a high significant decrease ($P < 0.001$) in the level of Mb-ATP as compared to the control group. But, the PPA, PPA+RISP and PPA+NL treated groups showed a statistically but not significantly increase in the Mb-ATP when compared to the PPA group.

Table (2) : Effect of different treatments by stinging nettle leaves (NL), roots (NR) and risperidone (RISP) drug on bioenergetics (adenosinetriphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP)) contents (ug/g wet tissues) in the Cortex, hippocampus and midbrain of rats induced by propionic acid (PPA).

	Groups	Cortex	hippocampus	midbrain
ATP	Control (CON)	43.8±0.68	25.4±0.420	31.4±0.210
	PPA	31.8±1.06 a***	25.8 ±0.728	23.8 ±0.515 a***
	PPA+RISP	37±0.99 a***b**	25.02±0.572	23.3±0.999 a***
	PPA+NL	28.3±1.68a***b*c***	24.5±1.13	24.2±0.927 a***
	PPA+NR	36.6±0.45a***b**d***	20.3 ±0.763 a***b***c***d***	21.8±0.870 a***d*
ADP	CON	24.7±0.332	15.2±0.610	19.6±0.118
	PPA	18.5±0.36a***	15.5±0.448	14.0±0.796 a***
	PPA+RISP	23.6±0.84 b***	15.9±0.679	13.4±0.408 a***
	PPA+NL	16.3±0.8 a***b*c***	15.7±0.877	13.8±0.665 a***
	PPA+NR	22.7±0.54 a*b***d***	11.4±0.277 a***b***c***d***	14.4±0.0542 a***
AMP	CON	15.8 ±0.422	9.1 ±0.099	9.3±0.491
	PPA	9.7±0.642 a***	7.8±0.386 a*	6.8±0.306 a**
	PPA+RISP	12±0.781 a***b*	7.2 ±0.568 a**	7.7±0.494 a*
	PPA+NL	9.9±0.608 a***c*	7.3 ±0.214 a**	7.3±0.629 a*
	PPA+NR	11.8 ±0.780 a***b*	6.3±0.374 a***b**	6.8±0.596 a**

Values are means± SE of six rats, a=significant difference compared with control group (CON), b= significant difference compared with propionic acid group (PPA), c=significant difference compared with propionic acid + Risperidone treatment group (PPA+RISP), d= significant difference compared with propionic acid + nettle leaves treatment group (PPA+NL), propionic acid +nettle roots (PPA+NR), *Significant level of probability ($P<0.05$), ** Significant level of probability ($P < 0.01$), *** Significant level of probability ($P <0.001$), Non-significance ($P \geq 0.05$) .

Table (2) indicated the presence of a significant decrease ($P < 0.001$) in the content of COR-ADP of the PPA administrated group and the PPA+NL treated group when compared to the CON group. Also, a significant

decrease ($P < 0.05$) was shown in COR-ADP contents in the PPA+NR treated group when compared to the CON group. On the other hand, the PPA+ RISP, and PPA+NR groups exhibited a high significant elevation ($P < 0.001$) in the level of COR-ADP when compared to the PPA group. Analyzing data in Table (2) indicated that there was no significant remarked in the PPA, PPA+RISP and PPA+NL treated groups when compared to the control group and the PPA group. On other hand, there was a high significant depletion ($P < 0.001$) in the level of H-ADP in PPA+NR when compared to the CON and PPA treated groups. Moreover, there was a high significant decrease ($P < 0.001$) in Mb-ADP in all treated group when compared to the CON group.

Recorded value estimated that there was a great significant diminution ($P < 0.001$) in the COR-AMP level of PPA, PPA+NL, PPA+ RISP and PPA+ NR treated groups as compared to the CON group. While, a significant ($P < 0.05$) increase was noticed in the PPA+RISP, and PPA+NR treated when compared to the PPA group. Also, the PPA+NR showed a high significant decrease ($P < 0.001$) in the H-AMP contents as compared to the CON group. Moreover, The PPA+RISP, and PPA+NL exhibited a significant ($P < 0.01$) decrease in the level of H-AMP when compared to the CON group. However, the PPA group showed a significant ($P < 0.05$) decrease in the level of H-AMP when compared to the CON group. Also, PPA+NR group exhibited a significant decrease ($P < 0.01$) in H-AMP when compared to the PPA group. Regarding midbrain, there was a significant decrease ($P < 0.01$) in the PPA, PPA+NR treated groups in Mb-AMP contents when compared to the CON group. Also, the PPA+RISP and PPA+NL treated group exhibited a significant decrease ($P < 0.05$) in the Mb-AMP contents when compared to the CON group. On other side, the PPA+RISP, PPA+NL, PPA+NR treated groups showed a statistically but not significantly increase in the level of Mb-AMP when compared to the PPA group as shown in Table (2).

Regarding the three-box chamber, data in Figure (1) showed that the PPA, PPA+NL and PPA+NR treated groups exhibited a high significant decrease ($P < 0.001$) in the number of entries when compared to the CON group. Also, the PPA+RISP treated group exhibited a significant decrease ($P < 0.01$) in the number of entries when compared to the CON group.

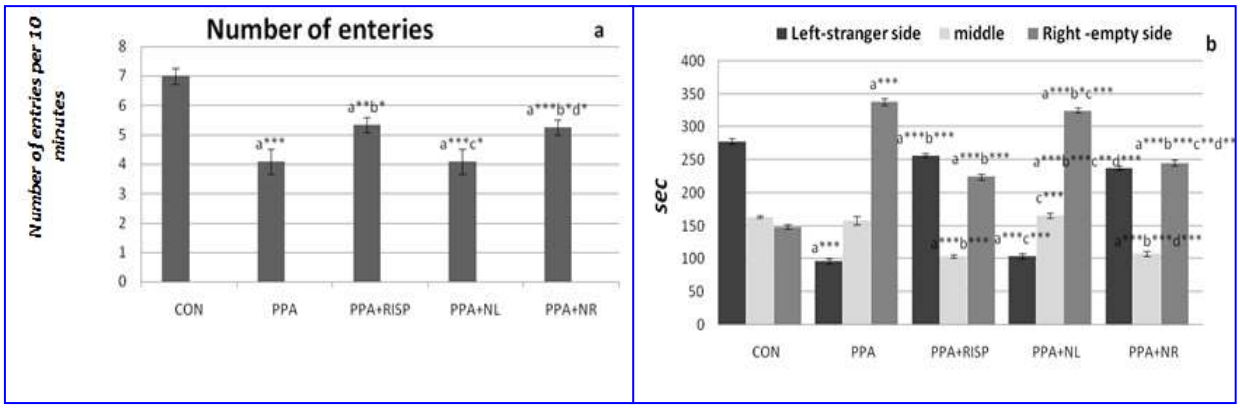

Fig. (1): Effect of different treatments stinging nettle (leaves(NL), roots(NR) and risperidone (RISP) drug on the number of entries to the chambers per ten minutes (a); the sociability preference in different treated groups represented by time spent in three box chamber maze (b).

Values are means± SE of 12 rats, a=significant difference compared with control group(CON), b=significant difference compared with propionic acid group (PPA), c=significant difference compared with propionic acid + Risperdone treatment group (PPA+RISP), d= significant difference compared with propionic acid + nettle leaves treatment group(PPA+NL), propionic acid +nettle roots (PPA+NR), *Significant level of probability ($P<0.05$), ** Significant level of probability ($P < 0.01$), *** Significant level of probability ($P <0.001$), Non-significance ($P \geq 0.05$) .

In contrast, the PPA+RISP and PPA+NR treated groups showed a significant ($P < 0.05$) increase in the number of entries in comparison with the PPA group. Moreover, all the treated groups exhibited a high significant ($P < 0.001$) decrease in the time spent in the left-side with the stranger when compared to the CON group. However, the PPA+RISP and PPA+NR treated groups showed a significant ($P < 0.001$) increase in the time spent in the left –stranger side when compared to the PPA group. In contrast, the PPA and PPA+NL treated groups exhibited a statistically but not significantly change in the time spent in the middle chamber when compared to the CON group. While, the PPA+RISP and PPA+NR treatment induced a significant ($P < 0.001$) decrease in the time spent in the middle when compared to the CON and PPA treated groups. Regarding the time spent in the right-empty side, the PPA, PPA+RISP, PPA+NL and PPA+NR treatments caused a high significant ($P < 0.001$) increase when compared to the CON group. While, the PPA+RISP and PPA+NR treated groups exhibited a significant ($P < 0.01$) decrease in the time spent in the right-empty side when compared to the PPA group. Also, PPA+NL showed a significant ($P < 0.05$) decrease in the time spent in the right-empty side in comparison with the PPA group. The stereotype activities and memory were assessed through the number of alternation and the number of correct alternation and they percentage in Y maze as shown in Figure (2). Data showed that all the treated groups exhibited a high significant ($P < 0.001$) decrease in the number of arm entries when compared to the CON group. While, the PPA+RISP and PPA+NR treated groups showed a significant ($P < 0.001$) increase in the number of arm entries when compared to the PPA group. Moreover, all the treated groups exhibited a high significant ($P < 0.001$) decrease in the number of correct alternations when compared to CON group. In contrast, the PPA+RISP and PPA+NR treatment induced a significant ($P < 0.001$) increase in the number correct alternations when compared to the PPA group. While, the PPA, PPA+NL treatments caused a significant ($P < 0.001$) increase in the percentage of alternations when compared to the CON group. In contrast, the PPA+NR and PPA+NR treated groups showed a statistically but not significantly increase in the percentage of alternations when compared to the CON group. Also, the PPA+RISP and PPA+NR treatment induced a significant ($P < 0.001$) decrease in the percentage of alternations as compared to the PPA group. While all the treated groups showed a statistically but not significantly increase in the percentage of correct alternations in comparison with CON and PPA groups.

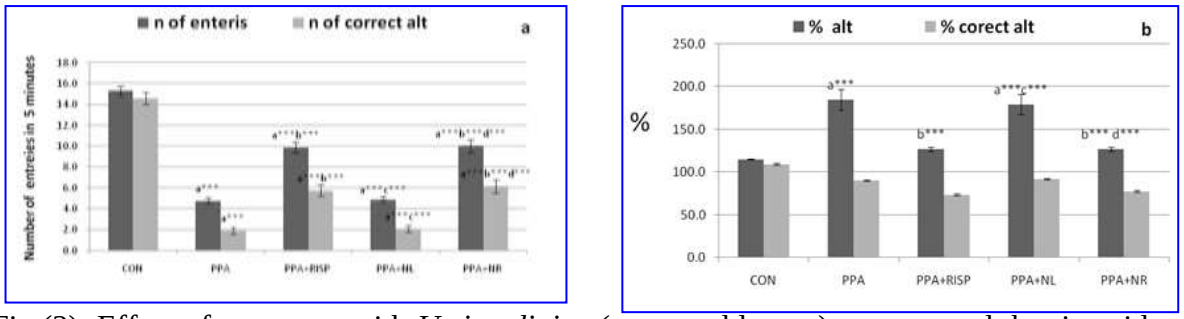

Fig.(2): Effect of treatment with *Urtica dioica* (roots and leaves) extracts and the risperidone drugs on the rat performance in Ymaze number of arm entries/ 5 min and correct alternations (a) and percentage of alternation and correct alternations (b) of the control and different treated groups.

Values are means± SE of 12 rats, a=significant difference compared with control group(CON), b= significant difference compared with propionic acid group (PPA), c=significant difference compared with propionic acid + Risperidone treatment group(PPA+RISP), d= significant difference compared with propionic acid + nettle leaves treatment group(PPA+NL), propionic acid +nettle roots (PPA+NR), *Significant level of probability($P<0.05$), ** Significant level of probability ($P < 0.01$), *** Significant level of probability ($P <0.001$), Non-significance ($P \geq 0.05$) .

DISCUSSION

The present data revealed that the systematic treatment with PPA produced a significant reduction in the three monoamines in the cortex and midbrain but, in hippocampus reduction occurs in dopamine only when compared to the control group. The present findings agreed with Nankova *et al*. (2014); Al-Salem *et al*. (2016); Shams *et al*. (2019). They reported that treatment of propionic acid reduced monoamines in the brain tissues. This may be due to the effect of PPA on tyrosine hydroxylase enzyme (Decastro *et al.*, 2005) which is like the action of butyrate short chain fatty acids that have the property to alter tyrosine hydroxylase gene expression. Tyrosine hydroxylase (TH) enzyme is responsible for monoamine biosynthesis transmitter and propionic acid may decrease it via reduce histone acetylation (Liu *et al.*, 2014).

Meyer *et al*. (2006) gave another explanation for the action of PPA on brain monoamine neurotransmitters, where it elevates monoamine oxidase A (MAO-A) activity in the brain which causes the depletion. Therefore, the inhibition of MAO-A activity could prevent the breakdown of monoamine neuro-transmitters and contribute to the increase of neurotransmitters in the synaptic cleft (Hamon and Blier, 2013). MAO-A are group of neuromodulator enzymes that break down neurotransmission after transmitting signals to avoid synaptic overcrowded and help synapses reach balance state (Béroule, 2018).

Deficiency in neuromodulator enzymes may be due to MOA-A gene which shows allelic variant property that reflects variation in function. Deckert *et al*. (1999) mentioned that if MOA-A gene contains three repeated allele, it will show low action but when contains the repeated allele number four it turns its opposite main function. This explains the deficiency of this enzyme among autistic children. Interestingly, it is very sensitive to environmental change (Meyer *et al*., 2009) and start to increase in brain at childhood age (2 to 4) in the same time when autism symptoms start to appear.

Miller and Timmie (2009) indicated that the elevation of cytokines in brain cells disrupt the synthesis and the reuptake of monoamine neurotransmitters. Two mechanisms prove these hypotheses the first mechanism including administration of cytokines to animals which influence monoamine neurotransmitter metabolism (Felger *et al.*, 2007; Anisman *et al*., 2008). The second mechanism drugs that affect monoamine metabolism produced cytokines in brain cells (Bull *et al*., 2008). Induction of cytokines such as IL_6 which increase as a result of injection PPA (Mac Fabe *et al*., 2011) produce indolamine 2, 3-dioxygenase (IDO) enzyme (Fujigaki *et al.*, 2006) that have the capacity to lysis the amino acid tryptophan precursor of serotonin into kynurenine that converted to kynurenic acid in astrocytes and microglia which will inhibit the production of 5-HT (Dantzer *et al*., 2008). kynurenic acid inhibits the release of glutamate which lead to inhibition of dopamine whose release in a part of glutamateric activity (Borland and Michael, 2004).

Nitricoxide (NO) elevation is associated with injection of PPA affecting the dopamine synthesis (Kitagami *et al.*, 2003). Accumulation of NO inside the cell occur by the action of BH4 enzyme cofactor (tetrahydrobiopterin) which is also have a curial role in the synthesis of dopamine via hydroxylation of tyrosine into L-3,4-dihydroxyphenylalanine (L-DOPA) and is the rate-limiting enzyme in DA synthesis.

Dopamine role in the cortex is responsible for behavior flexibility and cognitive control (Naneix *et al*., 2009). Increase or decrease in dopamine content can alter its main function (Del Campo *et al*., 2011; Ali and Elgoly, 2013; Hegazy *et al.*, 2015). Reduction of DA and NE is associated with attention-deficit hyperactivity disorder that linked to the

decrease in cortex activity (Zhang *et al*., 2017). Dopaminergic loss is a pivotal pathophysiology mechanism, giving rise to corticostriatal dysfunction, i.e. indirect pathway overactivity and direct pathway hypoactivity. It has also been revealed that different degrees of dopaminergic loss exert contrasting effects on the maintenance of two distinct types of corticostriatal synaptic plasticity, in the medium spiny neurons of the striatum (MSN). In particular, the corticostriatal long-term depression in MSNs is not altered by incomplete (approx. 75%) dopamine depletion, whereas the cortico-striatal is critically affected (Moghaddam *et al*., 2017).

Microglial over-activation has also been implicated as a potential felon mediating mood symptom via decreasing monoamines during elevated levels of inflammatory cytokines. More specifically, TNF-α and IL-1β are potent activators of microglia as part of the innate immune system (Harry and Kraft, 2012). Microglia over activation may associated with over-pruning of neural circuits, reduce neuroplasticity and ultimately disfunction of the neuronal circuits leading to impaired cognition and emotional regulation on a functional level (Rosenblat *et al*., 2014). Further, microglia activation impairs glutamate metabolism leading to alteration of glutamate levels and glutamate receptor activation (Hashimoto *et al.*, 2013).

Regarding RISP, in the present study there was an increase in the content of DA and 5-HT, however a statistically but not significantly difference was noticed in the content of NE in cortex tissues when compared to the PPA group. Moreover, RISP showed a significant increase in dopamine value only in hippocampus when compared to the PPA group. Although, our data revealed no effect of RISP on midbrain monoamines as compared to PPA group. These results could explain by the effect of RISP on DA receptors which depend on the dose (Moran-Gates *et al*., 2007). Our results in cortex cells explain the action of RISP as a blocker to α_1 5-HT_{A2} and α_2D_2 receptors (Aghajanian and Marek, 2000). The present results are in consistent with Kaminiska *et al*. (2018), Del Acro and Mora (2008), Ichikawa *et al*. (1998), (Meltzer *et al.* (2002) who found that RISP raise the level of DA more than the level of 5-HT and suggested that RISP was blocking the presynaptic D_2 receptor hence elevated DA neural terminal via partial working on antagonistic 5-HT_{1A} receptors and weak antagonist at 5-HT_{2c} receptors. Increase in the level of DA is due to the action of RISP on the 5 -HT_{1A} receptors agonists which mediate indirectly through GABAergic in VAT suppressing these interneurons (Wedzony *et al*., 1996).This may explan the present result in hippocampus which showed elevation in DA only, so RISP has a high affinity for 5-HT_{2A} receptors by blocking all that located on GABAergic interneurons in the frontal cortex. Elevation in the level of 5-HTmay be due to disinhibition of glutamatergic efferent pathway that also lead to DA release from raphe nuclei (Santana *et al.*, 2004).

Elevation of dopamine only in hippocampus in the present work may be due to the action of RISP to elevate DA is greater than 5-HT. Dopamine is the only monoamine that decrease in the PPA treated rats in this area. But monoamines in midbrain have not statically increase when compared to the PPA treated rats because its area of synthesis is not affected by RISP. It mainly works as blocker to receptors in cortex and cause neurodegenerative (loss in dopamine neuron) in midbrain area by reduce tyrosine hydroxylase enzyme (Reynolds *et al.*, 2011).

As for NL extract and NR extract, the results revealed that NL extract has poor effect on the brain monoamines except its elevated DA in midbrain when compared to the PPA group. That's may

be due to nettle leaves contain 5% of alkaloids (Skalozubova and Reshetova, 2013). It works as monoamine oxidase-A inhibitor (Zhang *et al*., 2018) and a MOA-B inhibitor (Mazzio *et al*., 2013). Enzymes work together and very important in catabolism of dopamine and its precursor like phenylalanine, tyrosine and tryptamine (Kalgutkar *et al*., 2001) which lead to decrease in dopamine. But inhibitor enzymes prevent catabolism which lead to increase in dopamine. Alkaloids results in the interaction with the Paired Associative Stimulation (PAS) of AChE, especially with Trp279 of PAS (Tang *et al*., 2009) which leads to an increase of the acetylcholine level and improved learning and memory abilities. Pharmacological effect that combines enhancement of cholinergic neurotransmission with a decrease in the pro-aggregating action of AChE (Zhang *et al*., 2018).

On the contrary, NR extract revealed a significant effect on monoaminergic system on NE, DA and 5-HT in cortex, and 5-HT in midbrain. These results could explain by the neuroprotective effect of UD. it can raise the content of DA and 5-HT in prefrontal cortex according to Hornick *et al.* (2011). It contains 5-HT precursor like 5-hydroxytryptamine, acetylcholine, choline, acetyltransferase and serotonin (Nahata and Dixit 2014 and Patel *et al*., 2016). Also, a possible explanation to nettle root effect on monoamine in our results was shown by Bisht *et al*. (2016). Inhibition of the MAO activity is very important in upregulating the levels of neuroactive amine such as dopamine, serotonin, and norepinephrine in the brain (Ademosun *et al*., 2016).

Urtica dioica contains flavonoids (Akbay *et al.,* 2003) and phenolics (Ioana *et al.,* 2013), flavonol glycosides (kaemferol-3-O-glucoside and -3-O-rutinoside; quercetin-3-O-glucoside and −3-Orutinoside; isorhamentin-3-O-glucoside; −3-O-rutinoside; and −3-oneohesperidoside (Chaurasia and Wichtl, 1987), some of which are major contributors in the antioxidant activity of *Urtica dioica*. Extract of nettle (*U. dioica*) has been recently indicated to show free radical scavenging activity (Ghaima *et al*., 2013). The HPLC analysis showed the presence of a bioactive marker, like ferulic acid which was reported to be a phenolic compound (Bisht *et al*., 2016) that have a neuroprotective effect (Hassanzadeh *et al*., 2018). Plants containing polyphenolic compounds have been reported to inhibit MAO activity (Oboh *et al.,* 2016). There is a strong correlation between total phenolic content and biological activities (Aliyazıcioglu *et al*., 2013; Oboh *et al*., 2017). This result revealed that phenolic compound may play an important role in the treatment of neurological disorders associated with depression and could prevent neurodegeneration in autism patients due to the structural similarities between phenolic compounds and synthetic inhibitors of these enzymes especially their hydrophobic component and phenolic rings (Benamar *et al*., 2010 and Nebbioso *et al*., 2012). Many natural effective antioxidant compounds such as flavonoids, phenolics, and polyphenols have neuroprotective role in various nervous system disorders by reducing oxidative stress induced mitochondrial dysfunction by decreasing the production of Bax and Bad protein, favoring an increase in the Bcl2–BclXL/Bax–Bak ratio (Mandel and Youdim, 2004).

The present data revealed that injection of PPA to the rats caused a decrease in bioenergetics (ATP, ADP and AMP) in cortex and midbrain but depletion occur in AMP in hippocampus when compared to the control group. Frye *et al.* (2016) measured ATP in the cell line PC_{12} and they found that at normal physiological condition with optimal dose of PPA, it shows a benefit role in mitochondria metabolism. Even if mitochondria expose to high dose of PPA with a continuous period it still benefitable by act as a fuel increasing level of ATP,

the final product of its metabolism up to 48 hours only. However, a reduction reported in the level of ATP due to a higher concentration and long period is trigger ROS (Villar *et al*., 2013) by PPA which metabolized to propionyl-CoA that access the CAC as succinyl-CoA. At physiological concentrations, this adds substrates to the CAC and boost mitochondrial function. However, high levels of succinyl-CoA, especially for a prolonged period of time, can inhibit CAC enzymes and over utilize acetyl-CoA, both of which might result in mitochondrial dysfunction, presumably by reducing the production of nicotinamide adenine dinucleotide, resulting in a decrease in ETC complex I function (Frye *et al*., 2015; 2016).

RNS, when present, can react with PPA to produce 3NP, a compound that strongly inhibits mitochondrial function through irreversible inhibition of succinate dehydrogenase (Francis *et al.,* 2013). Inhibition of succinate dehydrogenase shuts down the CAC from the succinate onward. Beneficial effects have been seen in brain after treatment with allopurinol or febuxostat to inhibit xanthine oxidoreductase, which catalyzes hypoxanthine (Johnson *et al*., 2019).

Regarding RISP the present result illustrated reduction in the three bioenergetics in cortex when compared to the control group while, showed a significant increase in the three bioenergetics when compared to the PPA group. In hippocampus decrease in AMP when compared to the control group. While, no change in the level of bioenergetics when compared to the PPA group Moreover, in midbrain decrease in all bioenergetics when compared to PPA group and control group. The current result agreed with the results of Liddle *et al*. (2000) and Lane *et al*. (2004). Reduction in bioenergetics in different area is related risperidone extra-pyramidal side effects.

The NL showed no change in the three bioenergetics in cortex, hippocampus and midbrain when compared to the PPA group. While, the NR groups exhibited a significant increase in the three bioenergetics in the cortex tissues, but a decrease was shown in hippocampus with no change in midbrain when compared to PPA group. Nettle root restoration of the bioenergetics levels may explain by the feluric acid (FA) which is one of the main components of NR (Bisht *et al.,* 2016). Recent research suggested that FA can regulate CAC circulatory dysfunction by increasing the ATP level in the limbic area of the brain of mice via activation of genes related to energy metabolism (Sasaki *et al*., 2019) and the action of NR to decrease NO and MDA and proinflammatory cytokines that may be help in regulation of mitochondrial functions (Bisht *et al.,* 2016; Ghasemi *et al*., 2019).

Previous studies have been outlined that propionic autistic like rat's model exhibited autism-like symptoms especially social defect which is the most characteristics' related to autism (Mirza and Sharma, 2018; Shams *et al.,* 2019). Similar results were obtained in the current study, where analysis of social behavior test using three box chamber apparatus revealed that PPA-treated rats showed defect in social behaviors when compared to the control group that including the time spent with the stranger who significantly lower in PPA treated rats than control group. The possible mechanism behind that behavior was that DA and 5-HT neurotransmission in the meso-corticolimbic pathways control social behaviors and social cognition of humans and animals (Kiser *et al.,* 2012). In human studies, both decrease and increase of 5-HT and DA transmission signals such as 5-HT metabolite depletion and SSRI treatments which implicated in social defect (Rot *et al*., 2006).

The present data revealed a decrease in the content of serotonin and

dopamine in cortex of PPA treated rat when compared to control which explain the behavior defect. The ventral tegmental area and the substantia nigra two dopaminergic neurons groups that projected from midbrain may be implicated in controlling behavior (Haber *et al.*, 2015). For social defect behavior, the decreased dopamine in mesocortico-limbic (MCL) circuit cause (MCL) dysfunction which will lead to decrease dopamine in the prefrontal cortex. These results were confirmed by our result for cortex dopamine contents in PPA treated rats. This decrease in COR-DA could alter reward and motivation and decision-making interaction which impacts social cognition which lead to social deficits (Chevallier *et al*., 2012). Also, social defected animal is characterized by low ATP (Liu *et al*., 2017). These results were confirmed by great reduction of bioenergetics (ATP, ADP and AMP) in different brain area (cortex, hippocampus and midbrain) of PPA treated rat when compared to the CON group as shown in the present work.

RISP could modify the social behavior defect produced by PPA due to its profile as a 5-HT2 antagonist, since these serotonergic receptors have been related to social interaction behavior (File and Seth, 2003). This was clear in increasing the time spent exploring stranger rat in three box chamber maze. Treatment with risperidone decreased aggressive behavior (Moechars *et al*., 1998). It also corrects the aggression induced by social isolation in male mice (Uchida *et al*., 2009) and the attack behavior in male albino mice (Rodríguez-Arias *et al.*, 1998). Risperidone has also been found to enhance pro social behavior in children with disruptive behavior and sub-average IQ (Snyder *et al*., 2002). Recent findings have shown that atypical antipsychotic treatment enhances the gene expression of oxytocin which is associated with the promotion of interpersonal trust (Keri *et al*., 2009). The cognitive behavioral mechanism of how atypical antipsychotic treatment improves social relationships remains unclear. Together, we postulate that atypical antipsychotic treatment, lowering the transmission of 5HT2A receptor, may effectively increase interpersonal trust and lead to improvement in social behavior.

The present investigation results indicated that NL has a poor effect in animal performance in social interaction test, and there was no change in the time spent with stranger when compared to PPA group. On contrast, it increased the time spent in the empty room with no increase in monoamine neurotransmitter or bioenergetics and increased pro inflammatory cytokines that has a negative effect in emotion and social behavior in animals. On the other hand, NR decreased the time spent in the empty room and increased the time spent with stranger which mean enhance social interaction of animal that was altered by PPA. This may be due to NR increases DA, and 5 -HT and reduces NO and MDA and increases bioenergetics and reduces Pro-inflammatory cytokines that implicated in impaired social interaction (Ghasemi *et al*., 2019).

The current results for PPA treated rat showed a reduction in spontaneous alt and the percent of correct alt in Y maze task when compared to control group. This result agreed with Mirza and Sharma (2018) which reflected short memory loss and abnormal behavior related to repetitive behavior. Stereotypic behavior may result from dopamine reduction in midbrain through dysfunctional nigro-striatal-cortical pathway neuronal circuit involved in cognitive processes such as spatial working memory. Many of the autistic children behavior insists in routines, they refuse change a known path (Mirenda *et al*., 2010). That a second typical symptoms of ASD is repetitive and restricted behaviors (Moy *et al*., 2008) which may be due to DA or 5-HT decrease in the hippocampus and midbrain. It has been

reported that depletion of 5-HT in the brain produces an impairment of short-term memory but not of long-term memory (Hritcu *et al*., 2007) especially depletion of prefrontal 5-HT (Clarke *et al.*, 2004) and inhibitory effect of 5-HT on other neurotransmitters involved in this process, such as norepinephrine and acetylcholine (Bell *et al.*, 2001). Such inhibition could facilitate the acquisition of information within short-term memory (Masaki *et al.,* 2006). Like any other neurotransmitter, the activity of 5-HT is mediated by specific receptors. Accordingly, the synaptic and physiological effects of serotonergic synapses depend on the type of receptor that is stimulated in the synapse. Likewise, these synapses can also be influenced by possible interactions between these serotonergic terminals and other neurotransmitter systems such as the cholinergic system in the hippocampus, cortex and striatum, where both systems cooperate in the regulation of cognitive functions. The 5HT1A receptors are closely associated with learning and memory (Meneses and Perez-Garcia, 2007). Transmission mediated by 1A receptors in the raphe complex, amygdala, septum, hippocampus and cerebral cortex, in relation to cognitive processes (Meneses, 2015). The 5HT1A receptors are present in 60% of the prefrontal pyramidal neurons and in 25% of the GABAergic interneurons (Santana *et al*., 2004). Like 5-HT, DA is widely distributed in brain regions closely associated with learning and memory processes, including, the prefrontal cortex, hippocampus and striatum. The activity of the working memory is in the prefrontal cortex. Previous study revealed that the depletion of DA produces an impairment of working memory (Surmeier, 2007).

It has been reported that the intra-hippocampal application of D2 receptor agonists improves the performance of spatial working memory, while the antagonist blockade of these receptors hinders its efficient performance (Wilkerson and Levin, 1999). The intra-cortical application of D1 receptor antagonists produces an impaired performance of spatial working memory (Sawaguchi and Goldman-Rakic, 1991) in rats (Seamans *et al*., 1995).

Regarding RISP, the present results showed that RISP attenuate the action of PPA in increase spontaneous alternation and percent of correct alt. The present results agreed with Torres-Lista *et al*. (2019). Despite dopamine D2 receptor blockade impairs spatial learning and memory (Beninger, 2006) in most novel antipsychotic drugs, RISP has a highest ratio of serotonin 5- HT2 receptor binding to D2 binding (Hertel, 2006). In addition, risperidone has moderately high affinity for D2 receptors and a very low affinity for dopamine D1 receptors (Bymaster *et al.*, 1996). The dose of risperidone used in the current study was relatively low. Counterbalance the D2 stimulation, thereby reducing the occurrence of spatial orientation impairments and could attenuating stereotyped behaviors with similar result in mouse model for autism (Silverman *et al.*, 2010).

The present results indicated that nettle leaves have a poor effect on the animal performance in Y maze task when compared to the PPA which may be due to it is neither working on monoamine neurotransmitter system nor bioenergetics system that end up with no change in the result of spontaneous alternation and percent of correct alternation. On other hand, nettle root increased the number of alternations and number of correct alternations in Y maze when compared to PPA treated groups. Because NR elevated the level of monoamines neurotransmitter (5-HT, NE, DA) in the prefrontal cortex and midbrain which have a high impact on spatial memory and learning and attenuate stereotype behavior produced by PPA. There is an evidence that in the recovery of

information related to conditioned responses in a passive avoidance paradigm in rats, the activity of DA is involved in mechanisms of information processing that determine the behavioral strategy, while 5-HT activity is more closely related with the emotional mechanisms that underlie memory (Molodtsova, 2006). The levels of DA and 5-HT in the prefrontal cortex and midbrain are involved in cognitive functions associated with behavioral reinforcement and are activated concomitantly with activation of both dopaminergic and serotonergic activity. It has been demonstrated that DA differentially affects the 'working' component of short-term memory and that in the striatum both DA and 5-HT are released only in relation to the working memory component (Karakuyu *et al*., 2007). There is evidence that DA release is mediated by serotonergic activity both in the prefrontal cortex where it is stronger as well as in the striatum. The present results are in consistent with the results of Patel and Udayabanu (2014) who indicated that nettle extract attenuates the memory dysfunction.

REFERENCES

Ademosun, A.O.; Oboh, G.; Olupona, A.J.; Oyeleye, S.I.; Adewuni, T.M., and Nwanna, E.E. (2016). Comparative study of chemical composition, in vitro inhibition of cholinergic and monoaminergic enzymes, and antioxidant potentials of essential oil from peels and seeds of sweet orange (*Citrus sinensis* L. Osbeck) Fruits. J. Food Biochem., 40(1):53-60. doi:10.1111/jfbc.12187.

Aghajanian, G.K. and Marek, G.J. (2000). Serotonin model of schizophrenia emerging role of glutamate mechanism. Brain Res. Rev; 31: 302-312.

Aguirre, M. and Venema, K. (2017). Challenges in simulating the human gut for understanding the role of the microbiota in obesity. Benef. Microbes; 8(1):31-53.

Akbay, P.; Basaran, A.A.; Undeger, U. and Basaran, N. (2003). In vitro immunomodulatory activity of flavonoid glycosides from *Urtica dioica* L. Phytother. Res., 17(1):34–37.

Ali, E.H.A and Elgoly, A.H.M. (2013). Combined prenatal and postnatal butyl paraben exposure produces autism-like symptoms in offspring: Comparison with valproic acid autistic model. Pharmacol. Biochem. Behav., 111: 102–110.

Aliyazıcıoglu, R.; Sahin, H.; Erturk, O.; Ulusoy, E. and Kolayli, S. (2013). Properties of phenolic composition and biological activity of propolis from Turkey. Int. J. Food Properties, 16(2):277–287.

Anisman, H.; Merali, Z. and Hayley, S. (2008). Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: Comorbidity between depression and neuro-degenerative disorders. Prog. Neurobiol., 85:1–74.

Bell,C.; Abrams, J. and Nutt, D. (2001). Tryptophan depletion and its implications for psychiatry. Br. J. Psychiatry, 178: 399–405.

Benamar, H.; Rached, W.; Derdour, A. and Marouf, A. (2010). Screening of Algerian medicinal plants for acetylcholinesterase inhibitory activity. J. Biological Sci., 10(1):1–9.

Beninger, R.J. (2006) Dopamine and incentive learning: a framework for considering antipsychotic medication effects. Neurotox Res., 10: 199- 209.

Béroule, D.G. (2018). Offline encoding impaired by epigenetic regulations of monoamines in the guided propagation model of autism. BMC Neurosci, 19(1):80. https://doi.org/10.1186/s12868-018-0477-1.

Bisht, R.; Joshi, B.C.; Kalia, A.N. and Prakash, A. (2016). Antioxidant-

Rich Fraction of *Urtica dioica* mediated rescue of striatal mito-oxidative damage in mptp-induced behavioral, cellular, and neurochemical alterations in rats. Mol. Neurobiol., 54(7):5632-5645.

Bjørklund, G.; Meguid, N.A.; El-Bana, M.A.; Tinkov, A.A.; Saad, K.; Dadar, M.; Hemimi, M.; Skalny, A.V.; Hosnedlová, B.; Kizek, R.; Osredkar, J.; Urbina, M.A.; Fabjan, T.; El-Houfey, A.A.; Kałużna-Czaplińska, J.; Gątarek, P. and Chirumbolo, S. (2020). oxidative stress in autism spectrum disorder. Mol. Neurobiol.,57:2314–2332.doi:10.1007/s12035-019-01742-2

Blandina, P.; Efoudebe, M.; Cenni, G.; Mannaioni, P. and Passani, M.B. (2004). Acetylcholine, histamine, and cognition: two sides of the same coin. Learn. Mem., 11: 1-8.

Borland, L.M. and Michael, A.C. (2004). Voltammetric study of the control of striatal dopamine release by glutamate. J. Neurochem., 91:220–229.

Broer, J. and Behnke, B. (2002). Immunosuppressant effect of IDS 30, a stinging nettle leaf extract, on myeloid dendritic cells in vitro. J. Rheumatol., 29(4):659-66.

Bull, S.J.; Huezo-Diaz, P.; Binder, E.B.; Cubells, J.F.; Ranjith, G.; Maddock, C.; Miyazaki C.; Alexander, N.; Hotopf, M.; Cleare, A.J.; Norris, S.; Cassidy, E.; Aitchison, K.J.; Miller, A.H. and Pariante, C.M. (2008). Functional polymorphisms in the interleukin-6 and serotonin transporter genes and depression and fatigue induced by interferon-alpha and ribavirin treatment. Mol. Psychiatry, 14(12):1095-1104.

Bymaster, F.P.; Calligaro, D.O.; Falcone, J.F.; Marsh, R.D.; Moore, N.A.; Tye, N.C.; Seeman, P. and Wong, D.T. (1996). Radioreceptor binding profile of the a typical antipsychotic olanzapine. Neuro-psycho-pharmacol.,14:87- 96.

Celada, P.; Puig, M.V. and Artigas, F. (2013). Serotonin modulation of cortical neurons and networks. Front Integr. Neurosci., 7: 25.

Chacko, A.; Bedard, A.C.; Marks, D.J.; Feirsen, N.; Uderman, J.Z.; Chimiklis, A.; Rajwan, E.; Cornwell. M.; Anderson. L.; Zwilling. A. and Ramon, M. (2014). A randomized clinical trial of Cogmed Working Memory Training in school-age children with ADHD: a replication in a diverse sample using a control condition. J. Child. Psychol. Psychiatry, 55(3):247-55.

Chacko, B.;Culp, M.L.; Bloomer, J.; Phillips, J.; Kuo, Y.F.; Victor, Darley-Usmar, V. and Singal, A.K. (2019). Feasibility of cellular bioenergetics as a biomarker in porphyria patients. Mol. Genet. Metab. Rep., 19:100451.

Chaurasia, N. and Wichtl, M. (1987). Flavonol glycosides from *Urtica dioica*. Planta Med., 53(5):432–434.

Chevallier, C.; Kohls, G.; Troiani, V.; Brodkin, E.S. and Schultz, R.T. (2012). The Social Motivation Theory of Autism. Trends Cogn. Sci., 16(4): 231–239.

Choudhury, P.R.; Lahiri, S. and Rajamma, U. (2012). Glutamate mediated signaling in the pathophysiology of autism spectrum disorders. Pharmacol. Biochem. and Behav., 100:841–849.

Chugani, H.T; Behen, M.E.; Muzik, O.; Juhász, C.; Nagy, F. and Chugani, D.C. (2001). Local brain functional activity following early deprivation: a study of post-institutionalized Romanian orphans. Neuroimage, 14(6):1290-301.

Clarke, H.F.; Dalley, J.W.; Crofts, H.S.; Robbins, T.W. and Roberts, A.C. (2004). Cognitive inflexibility after prefrontal serotonin depletion. Science; 304: 878–880.

Dantzer, R.; O'Connor, J.C.; Freund, G.G.; Johnson, R.W. and Kelley, K.W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. Nat. Rev. Neurosci., 9:46–56.

DeCastro, M.; Nankova, B.B.; Shah, P.; Patel, P.; Mally, P.V.; Mishra, R. and La Gamma, E.F. (2005). Short chain fatty acids regulate tyrosine hydroxylase gene expression through a cAMP-dependent signaling pathway. Brain Res. Mol. Brain Res., 142(1):28–38.

Deckert, J.; Catalano, M.; Syagailo, Y.V.; Bosi, M.F.; Okladnova, O.V.; Di Bella, D.J.; Nöthen, M.M.; Maffei, P.; Franke, P.; Fritze, J.; Maier, W.; Propping, P.; Beckmann, H.K.; Bellodi, L. and Lesch, K.P. (1999). Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. Hum. Mol. Genet., 8(4):621–624.

Del Arco, A. and Mora, F. (2008). Prefrontal cortex-nucleus accumbens interaction: in vivo modulation by dopamine and glutamate in the prefrontal cortex. Pharmacol. Biochem. Behav., 90 (2): 226-235. doi:10.1016/j.pbb. 2008.04.011.

Del Campo N, Chamberlain SR, Sahakian BJ, and Robbins TW. (2011). The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit / hyperactivity disorder. Biol. Psychiatry; 69(12): e145-57. doi: 10.1016/ j.biopsych.2011.02.036. Epub 2011 May

Felger, J.C.; Alagbe, O.; Hu, F.; Mook, D.; Freeman, A.A.; Sanchez, M.M.; Sanchez, M.M.; Kalin, N.H.; Ratti, E.; Nemeroff, C.B. and Miller, A.H. (2007). Effects of interferon-alpha on rhesus monkeys: A non-human primate model of cytokine-induced depression. Biol. Psychiatry, 62(11):1324–1333.

File , S. and Seth, P. (2003). A review of 25 years of the social interaction test. Eur. J. Pharmacol., 463: 35–53.

Francis, J.M.; Kiezun, A.; Ramos, A.H.; Serra, S.; Pedamallu, C.S.; Qian, Z.R.; Banck, M.S.; Kanwar, R.; Kulkarni, A.A.; Karpathakis, A.; Manzo, V.; Contractor, T.; Philips, J.; Nickerson, E.; Pho, N.; Hooshmand, S.M.; Brais, L.K.; Lawrence, M.; Pugh, T.; McKenna, A.; Sivachenko, A.; Cibulskis, K.; Carter, S.L.; Ojesina, A.I.; Freeman, S.; Jones RT, Voet D, Saksena, G.; Auclair, D.; Onofrio, R.; Shefler, E.; Sougnez, C.; Grimsby, J.; Green, L.; Lennon, N.; Meyer, T.; Caplin, M.; Chung, D.C.; Beutler, A.S.; Ogino, S.; Thirlwell, C.; Shivdasani, R.; Asa, S.L.; Harris, C.R.; Getz, G.; Kulke, M. and Meyerson, M. (2013). Somatic mutation of CDKN1B in small intestine neuroendocrine tumors. Nat. Genet., 45(12):1483-1486.

Frye, R.E.; Rose, S.; Chacko, J.; Wynne, R.; Bennuri, S.C.; Slattery, J.C.; Tippett, M.; Delhey, L.; Melnyk, S.; Kahler, S.G. and MacFabe, D.F. (2016) Modulation of mitochondrial function by the microbiome metabolite propionic acid in autism and control cell lines. Transl. Psychiatry, 6 (10): e927; doi:10.1038/tp.2016.189.

Frye, R.E.; Slattery J, MacFabe DF, Allen-Vercoe, E.; Parker, W.; Rodakis, J.; Adams, J.B.; Krajmalnik-Brown, R.; Bolte, E.; Kahler, S.; Jennings,

J.; James. J.; Cerniglia, C.E. and Midtvedt, T. (2015). Approaches to studying and manipulating the enteric microbiome to improve autism symptoms. Microb. Ecol. Health Dis., 26: 26878.

Fujigaki, H.; Saito, K.; Fujigaki, S.; Takemura, M.; Sudo, K.; Ishiguro, H.; and Seishima, M. (2006). The signal transducer and activator of transcription 1 alpha and interferon regulatory factor 1 are not essential for the induction of indoleamine 2,3-dioxygenase by lipopoly-saccharide: Involvement of p38 mitogen-activated protein kinase and nuclear factor-kappaB pathways, and synergistic effect of several proinflammatory cytokines. J. Biochem.,139(4):655–662.

Ghaima, K.K.; Hashim, N.M. and Ali, S.A. (2013). Antibacterial and antioxidant activities of ethyl acetate extract of nettle (*Urtica dioica*) and dandelion (*Taraxacum officinale*). J. Appl. Pharm. Sci., 3 (05): 096-099.

Ghasemi, S.; Moradzadeh, M.; Hosseini, M.; Beheshti, F. and Sadeghnia, H.R. (2019). Beneficial effects of *Urtica dioica* on scopol-amineinduced memory impairment in rats: protection against acetyl-cholinesterase activity and neuronal oxidative damage. Drug Chem. Toxicol., 42(2):167-175.

Haber, J.; Hartnett, E.; Allen, K.; Hallas, D.; Dorsen, C.; Lange-Kessler, J.; Lloyd, M.; Thomas, E. and Wholihan, D. (2015). Respond. Am. J. Public Health, 105(5): e3–e4.doi: 10.2105/AJPH.2015.302648

Hamon, M. and Blier, P. (2013). Monoamine neurocircuitry in depression and strategies for new treatments. Prog. Neuro-Psychopharmacol. Biol. Psychiatry; 45:54–63. doi: 10.1016/j.pnpbp.2013.04.009.

Harry, G.J. and Kraft, A.D. (2012). Microglia in the developing brain: a potential target with lifetime effects. Neurotoxicol., 33(2):191-206. http://dx.doi.org/10.1016/j.neuro.2012.01.012

Hashimoto, K.; Malchow, B.; Falkai, P. and Schmitt, A. (2013). Glutamate modulators as potential therapeutic drugs in schizophrenia and affective disorders. Eur. Arch. Psychiatry Clin. Neurosci; 263(5): 367-77. doi: 10.1007/s00406-013-0399-y.

Hassanzadeh, P.; Arbabi, E.; Atyabi, F. and Dinarvand, R. (2018). Ferulic acid-loaded nanostructured lipid carriers: A promising nano-formulation against the ischemic neural injuries. Life Sci.,193:64-76. doi: 10.1016/j.lfs.2017.11.046.

Hegazy, H.G.; Ali, E.H.A. and Sabry, H.A. (2016). The neuroprotective action of naringenin on oseltamivir (tamiflu) treated male rats. J. Basic Appl. Zool. (JOBAZ), (77): 83–90.

Hegazy, H.G.; Ali, E.H.A. and Elgoly, A.H.M. (2015). Interplay between pro-inflammatory cytokines and brain oxidative stress biomarkers: Evidence of parallels between butyl paraben intoxication and the valproic acid brain physiopathology in autism rat model. Cytokine, 71: 173–180.

Hertel, P. (2006) Comparing sertindole to other new generation antipsychotics on preferential dopamine output in limbic versus striatal projection regions: mechanism of action. Synapse, 60(7): 543-552.

Hornick, A.; Lieb, A.; Vo, N.P.; Rollinger, J.M.; Stuppner, H. and Prast, H. (2011). The coumarin scopoletin potentiates acetylcholine release from synaptosomes, amplifies hippocampal long-term potentiation and ameliorates

anticholinergic and age-impaired memory. Neurosci., 197: 280–292.

Hritcu, L.; Clicinschi, M. and Nabeshima, T. (2007). Brain serotonin depletion impairs short-term memory, but not longterm memory in rats. Physiol. Behav., 91: 652–657.

Ichikawa, J.; Kuroki, T.; Dai, J. and Meltzer, H.Y. (1998). Effect of antipsychotic drugs on extracellular serotonin levels in rat medial prefrontal cortex and nucleus accumbens. Eur. J. Pharmacol., 351(2):163–71.

Ioana, N.; Viorica, I.; Diana-Carolina, I. and Valeria, R. (2013). Preliminary research regarding the therapeutic uses of Urtica dioica l note ii. The dynamics of accumulation of total phenolic compounds and ascorbic acid. Farmacia, 61(2):276–283.

Jalili, C.; Salahshoor, M.R. and Naseri, A. (2014). Protective effect of Urtica dioica L against nicotine induced damage on sperm parameters, testosterone and testis tissue in mice. Iran J. Reprod. Med., 12(6): 401-408.

Johnson, T.A.; Jinnah, H.A. and Kamatani, N. (2019). Shortage of Cellular ATP as a Cause of Diseases and Strategies to Enhance ATP. Front Pharmacol., 10:98. doi: 10.3389/ fphar.2019.00098.

Kalgutkar, A.S.; Dalvie, D.K.; Castagnoli, N. and Taylor, T.J. (2001). Interactions of nitrogen-containing xenobiotics with monoamine oxidase (MAO) isozymes A and B: SAR studies on MAO substrates and inhibitors. Chem. Res. Toxicol., 14 (9): 1139–1162. doi:10.1021/tx010073b.

Kaminska, K.; Górska, A.; Noworyta-Sokołowska, K.; Wojtas, A.; Rogó, Z. and Gołembiowska, K. (2018). The effect of chronic co-treatment with Risperidone and novel antidepressant drugs on the dopamine and serotonin in the level of rats frontal cortex. Pharmacological Reports; 70(5): 1023-1031. doi:10.1016/j.pharep. 2018.04.009.

Karakuyu, D.; Herold, C.; Güntürkün, O.; and Diekamp, B. (2007). Differential increase of extracellular dopamine and serotonin in the "prefrontal cortex" and striatum of pigeons during working memory. Eur. J. Neurosci., 26: 2293–2302. doi:10.1111/j.1460-9568.007.05840.x

Keri, S.; Kiss, I. and Kelemen, O. (2009). Sharing secrets: Oxytocin and trust in schizophrenia. Soc. Neurosci., 4: 287–293.

Kirino, E. (2014). Efficacy and tolerability of pharmacotherapy options for the treatment of irritability in autistic children. Clin. Med. Insights. Pediatrics, 8:17-30. doi:10.4137/ CMPed.S8304. PMC 4051788. PM ID 24932108.

Kiser, D.; Steemers, B.; Branchi, I. and Homberg, J.R. (2012). The reciprocal interaction between serotonin and social behavior. Neurosci. Biobehav. Rev., 36(2):786-798.

Kitagami, T.; Yamada, K.; Miura, H.; Hashimoto, R.; Nabeshima, T. and Ohta, T. (2003). Mechanism of systemically injected interferon-alpha impeding monoamine biosynthesis in rats: Role of nitric oxide as a signal crossing the blood-brain barrier. Brain Res., 978:104–114.

Lane, A.M.; Terry, P.C. Beedie, C.J. and Stevens, M. (2004). Mood and concentration grid performance: The moderating effect of depressed mood. Int. J. Sport Psychol.,2: 133-145.

Liddle, H.A.; Rowe, C.L.; Diamond, G.M.; Sessa, F.M.; Schmidt, S. and Ettinger, D. (2000). Toward a developmental family therapy: the

clinical utility of research on adolescence. J. Marital and Family Therapy, 4:485–500.

Liu, D.; Qiu, H.M.; Fei, H.Z.; Hu, X.Y.; Xia, H.J.; Wang, L.J.; Qin, L.J.; Jiang, X.H. and Zhou, Q.X. (2014). Histone acetylation and expression of mono-aminergic transmitters synthetases involved in CUS-induced depressive rats. Experimental Biology and Medicine; 239: 330–336.

Liu, H.; Jiang, Y.; Luo, Y. and Jiang, W. (2006). A simple and rapid determination of ATP, ADP and AMP concentrations in pericarp tissue of litchi fruit by high performance liquid chromate-graphy. Food Technol. Biotechnol., 44(4):, 531-534.

Liu, Y.Y.; Zhou, X.Y.; Yang, L.N.; Wang, H.Y.; Zhang, Y.Q.; Pu, J.C.; Liu, L.X.; Gui, S.W.; Zeng, L.; Chen, J.J.; Zhou, C.J. and Xie, P. (2017). Social defeat stress causes depression-like behavior with metabolite changes in the prefrontal cortex of rats. PLoS One;12(4):e0176725.

MacFabe, D.F.; Cain, N.E.; Boon, F.; Ossenkopp, K.P. and Cain, D.P. (2011). Effects of the enteric bacterial metabolic product propionic acid on object-directed behavior, social behavior, cognition, and neuroinflammation in adolescent rats: relevance to autism spectrum disorder. Behav. Brain Res., 217:47.

Mandel, S. and Youdim, M.B. (2004). Catechin polyphenols: neuro-degeneration and neuroprotection in neurodegenerative diseases. Free Radic. Biol. Med., 37(3):304–31.

Masaki, D.; Yokoyama, C.; Kinoshita, S.; Tsuchida, H.; Nakatomi, K.; Yoshimoto, K. and Fukui, K. (2006). Relationship between limbic and cortical 5-HT neurotransmission and acquisition and reversal learning in a go/no-go task in rats. Psychopharmacol., 189: 249–258.

Mazzio, E.; Deiab, S.; Park, K. and Soliman, K.F. (2013). High throughput screening to identify natural human monoamine oxidase B inhibitors. Phytother. Res., 27(6):818–828.

McNamara, C.G.; Tejero-Cantero, Á.; Trouche, S.; Campo-Urriza, N. and Dupret, D. (2014). Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. Nat. Neurosci.,17(12):1658-1660. doi: 10.1038/nn.3843. Epub 2014 Oct 19.

Meltzer, H.; Singleton, N.; Lee, A.; Bebbington, P.; Brugha, T. and Jenkins, R. (2002). The social and economic circumstances of adults with mental disorders. London: Stationery Office

Meneses, A. and Perez-Garcia, G. (2007). 5-HT(1A) receptors and memory. Neurosci. Biobehav. Rev., 31(5): 705-27.

Meneses, A. (2015). Serotonin, neural markers and memory. Front Pharmacol., 6: 143. doi: 10.3389/fphar.2015.00143

Meyer, J.H.; Rusjan, P. and Voineskos, A.N. (2009). Brain monoamine oxidase A binding in major depressive disorder. Arch. Gen. Psychatry, 66(12):1304–1312.

Meyer, J.H.; Ginovart, N.; Boovariwala, A.; Sagrati, S.; Hussey, D.; Garcia, A.; Young, T.; Praschak-Rieder, N.; Wilson, A.A.; Houle, S. (2006). Elevated monoamine oxidase A levels in the brain: an explanation for the monoamine imbalance of major depression. Arch. Gen. Psychiatry, 63 (11): 1209–1216.

Miller, A.H. and Timmie, W.P. (2009). Mechanisms of cytokine-induced

behavioral change: Psycho-neuroimmunology at the translational interface Norman Cousins Lecture. Brain Behav. Immun., 23(2): 149–158.

Mirenda, P.; Smith, I.M.; Vaillancourt, T.; Georgiades, S.; Duku, E.; Szatmari, P.; Bryson, S.; Fombonne, E.; Roberts, W.; Volden, J.; Waddell, C.; Zwaigenbaum, L. *et al*. (2010). Validating the Repetitive Behavior Scale—Revised in young children with autism spectrum disorder. J. Autism Dev. Disord., 40:1521–1530.

Mirza, R. and Sharma, B. (2018). Selective modulator of peroxisome proliferator-activated receptor-α protects propionic acid induced autism-like phenotypes in rats. Life Sci., 214: 106-117. doi: 10.1016/ j.lfs.2018.10.045.

Moechars, D.; Gilis, M.; Kuiperi, C.; Laenen, I. and Van Leuven, F. (1998). Aggressive behaviour in transgenic mice expressing APP is alleviated by serotonergic drugs. Neuroreport., 9: 3561–3564.

Moghaddam MF, Validad A, Rakhshani T, and Assareh M. (2017). Child self-esteem and different parenting styles of mothers: a cross-sectional study Mahboubeh, Archives of Psychiatry and Psychotherapy; 1: 37–42.

Molodtsova, G.F. (2006). Different roles of dopamine and serotonin in conditioned passive avoidance response of rats. Zh. Vyssh. Nerv. Deiat. Im. I. P. Pavlova, 56(2):242-6.

Moran-Gates, T.; Grady, C.; Shik, P.Y.; Baldessarini, R.J. and Tarazi, F.I. (2007). Effects of risperidone on dopamine receptor subtypes in developing rat brain. Published in final edited form as: Eur. Neuropsychopharmacol., 17(6-7): 448–455.

Moy, S.S.; Nadler, J.J.; Poe, M.D.; Nonneman, R.J.; Nancy, B.; Young, N.B.; Koller, B.H.; Crawley, J.N.; Duncan, G.E. and Bodfish, J.W. (2008). Development of a mouse test for repetitive, restricted behaviors: relevance to autism. Behav. Brain Res., 188:178–194.

Muller, C.L.; Anacker, A.M.J. and Veenstra-VanderWeele, J. (2016). The serotonin system in autism spectrum disorder: From biomarker to animal models. Neuroscience 321: 24-41

Nadler, J.J.; Moy, S.S.; Dold, G.; Trang, D.; Simmons, N.; Perez, A.; Young, N.B.; Barbaro, R. P.; Piven, J.; Magnuson, T.R.; Crawley, J.N. (2004). Automated apparatus for quantitation of social approach behaviors in mice. Genes Brain Behav., 3(5):303-314.

Nahata, A. and Dixit, V.K. (2014). Evaluation of 5α reductase inhibitory activity of certain herbs useful as antiandrogens. Andrologia, 46(6):592-601.

Naneix, F.; Marchand, A.R.; Di Scala, G.; Pape, J.R., and Coutureau, E. (2009). A role for medial prefrontal dopaminergic innervation in instrumental conditioning. J. Neurosci., 29:6599–6606.

Nankova, B.B.; Agarwal, R.; MacFabe, D.F. and La Gamma, E.F. (2014). Enteric bacterial metabolites propionic and butyric acid modulate gene expression, including CREB-dependent catecholaminergic neuro-transmission, in PC12 cells - possible relevance to autism spectrum disorders. PLoS One; 9(8): e103740.

Nebbioso, N.; Pascarella, A.; Cavallotti, C. and Pescosolido, N. (2012). Monoamine oxidase enzymes and oxidative stress in the rat optic

nerve: Age-related changes. Int. J. Exp. Path., 93(6):401–405.

Oboh, G.; Ademiluyi, A.O.; Ogunsuyi, O.B.; Oyeleye, S.I.; Dada, A.F. and Boligon, A.A. (2017). Cabbage and cucumber extracts exhibited anticholinesterase, antimonoamine oxidase and antioxidant properties. J. Food Biochem., 41(3):1-7. e12358.

Oboh, G.; Adewuni, T.M.; Ademosun, A.O. and Olasehinde, T.A. (2016). Sorghum stem extract modulates Na+/K+-ATPase, ecto-5 - nucleotidase, and acetylcholine-esterase activities. Comp Clin Path; 25(4):49–756.

Pagel, P., Schubert, R., Wilhelm, C., and Wolf, H. U. (2000). Development of an HPLC-Method and Synthesis of 1,2,3,4-Tetrahydroisoquinolines as Reference Compounds for the Identification of Possible Neurotoxins in the Blood of Parkinson's Disease Patients. In : Neurotoxic Factors in Parkinson's disease and Related Disorders (pp. 111-114). Springer, Boston, MA.

Pajonk, F.G.. (2004). Risperidone in acute and long-term therapy of schizophrenia–a clinical profile. Prog Neuropsychopharmacol. Biol. Psychiatry, 28:15–23. 7.

Patel, S.S. and Udayabanu, M. (2014). *Urtica dioica* extract attenuates depressive like behavior and associative memory dysfunction in dexamethasone induced diabetic mice. Metabolic Brain Disease, 29(1): 121-130.

Patel, S.S.; Mahindroo, N. and Udayabanu, M. (2016). *Urtica dioica* leaves modulates hippocampal smoothened - glioma associated oncogene-1 pathway and cognitive dysfunction in chronically stressed mice. Biomedicine & Pharma-cotherapy, 83: 676-686.

Patel, S.S.; Parashar, A. and Udayaban, M. (2015). *Urtica dioica* leaves modulates muscarinic cholinergic system in the hippocampus of streptozotocin-induced diabetic mice. Metab. Brain Dis., 30:803–811

Reynolds, K.B.; MacGillivary, L.; Zettler, M.; Rosebush, P.I. and Mazurek, M.F. (2011). Role of the dopamine transporter in mediating the neuroleptic-induced reduction in tyrosine hydroxylase immune-reactive midbrain neurons. Brain Res.,1394:24-32.

Rodríguez-Arias, M.; Miñarro, J.; Aguilar, M.A.; Pinazo J. and Simón, V.M. (1998). Effects of risperidone and SCH 23390 on isolation-induced aggression in male mice. Eur. Neuropsychopharmacol., 8:95-103.

Roghani, M.; Joghataie, M.T.; Jalili, M.R.; and Baluchnejadmojarad, T. (2006). Time course of changes in passive avoidance and Y-maze performance in male diabetic rats. Iran. Biomed. J., 10(2): 99-104.

Rosenblat, J.D.; Cha, D.S.; Mansur, R.B. and McIntyre, R.S. (2014). Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog. Neuro-psychopharmacol. Boil. Psychiatry, 53:23-34.

Rot, M.; Moskowitz, D.S.; Pinard, G. and Young, S.N. (2006). Social behaviour and mood in everyday life: the effects of tryptophan in quarrelsome individuals. J. Psychiatry Neurosci., 31(4):253-62.

Sadacca, B.F.; Wikenheiser, A.M. and Schoenbaum, G. (2017). Toward a theoretical role for tonic norepinephrine in the orbitofrontal cortex in facilitating flexible learning. Neurosci., 345:124-129

Santana, L.F.; de Sá, M.F.; Ferriani, R.A.; de Moura, M.D.; Foss, M.C. and dos Reis, R.M. (2004). Effect of metformin on the clinical and metabolic assessment of women with polycystic ovary syndrome. Gynecol. Endocrinol., 19(2):88-96.

Santana, N.; Bortolozzi, A.; Serrats, J.; Mengod, G. and Artigas, F. (2004). Expression of serotonin 2A receptors in pyramidal and gabaergic neurons of the rat prefrontal cortex. Cereb Cortex; 14:1100–1109.

Sasaki, K.; Iwata, N.; Ferdousi, F. and Isoda, H. (2019). Antidepressant-like effect of ferulic acid via promotion of energy metabolism activity. Mol. Nutr. Food Res., 63(19):e1900327.

Sawaguchi, T. and Goldman-Rakic, P.S. (1991). D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science; 251(4996):947-50.

Seamans, J.K.; Floresco, S.B. and Phillips A.G. (1995). Functional differences between the prelimbic and anterior cingulate regions of the rat prefrontal cortex. Behav. Neurosci., 109:1063–1073.

Shams, S.; Foley, K.A.; Kavaliers, M.; MacFabe, D.F. and Ossenkopp K. (2019). Systemic treatment with the enteric bacterial metabolic product propionic acid results in reduction of social behavior in juvenile rats: Contribution to a rodent model of autism spectrum disorder. Develop. Psychobiol., 61(5): 688–699.

Siddiqui MF, Elwell C, and Johnson MH. (2016). Mitochondrial Dys-function in Autism Spectrum Disorders. Autism Open Access; 6(5):1000190.

Silverman, J.L.; Tolu, S.S.; Barkan, C.L. and Crawley, J.N. (2010). Repetitive self-grooming behavior in the BTBR mouse model of autism is blocked by the mGluR5 antagonist MPEP. Neuropsychopharmacol., 35: 976–989. doi: 10.1038/npp.2009.201

Skalozubova, T.A. and Reshetova, V.O. (2013). Leaves of common nettle (*Urtica dioica* L.) As a source of ascorbic acid (Vitamin C). World Appl. Sci. J., 28 (2): 250-253.

Snyder, R.; Turgay, A.; Aman, M.; Binder, C.; Fisman, S.; Carroll, A.; Risperidone Conduct Study Group (2002). Effects of risperidone on conduct and disruptive behaviour disorders in children with subaverage IQs. J. Am. Acad. Child Adolesc. Psychiatry, 41: 1026–1036.

Surmeier, D.J.; Ding, J.; Day, M.; Wang, Z. and Shen, W. (2007). D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. Trends in Neurosciences; 30 (5): 228–235.

Tang, H.; Wei, Y.B.; Zhang, C.; Ning, F.X.; Qiao, W.; Huang, S.L.; Ma, L.; Huang, Z.H. and Gu, L.Q. (2009). Synthesis, biological evaluation and molecular modeling of oxoisoaporphine and oxoaporphine derivatives as new dual inhibitors of acetylcholine-esterase/ butyrylcholinesterase. Eur. J. Med. Chem.,44(6): 2523-2532.

Torres-Lista, V.; López - Pousa, S., and Giménez-Llort, L. (2019). Impact of chronic risperidone use on behavior and survival of 3xTg-AD mice model of Alzheimer's disease and mice with normal aging. front. Pharmacol., 10:1061.

Uchida, N.; Egashira, N.; Iwasaki, K.; Ishibashi, A.; Tashiro, R.; Nogami, A.; Manome, N.; Abe, M.; Takasaki, K.; Mishima, K.; Ta kata, J.; Oishi, R.; Nishimura, R. and Fujiwara, M. (2009).

Yokukansan inhibits social isolation-induced aggression and methamphetamine-induced hyper-locomotion in rodents. Biol. Pharm. Bull., 32: 372–375. doi: 10.1248/bpb.32.372

Villar, J.; Altman, D.G.; Purwar, M.; Noble, J.A.; Knight, H.E.; Ruyan, P.; Cheikh, I.L.; Barros, F.C.; Lambert, A.; Papageorghiou, A.T.; Carvalho, M.; Jaffer, Y.A.; Bertino, E.; Gravett, M.G.; Bhutta, Z.A. and Kennedy, S.H. (2013). The objectives, design and implementation of the intergrowth-21st Project. BJOG; 2:9-26. doi: 10.1111/1471-0528.12047.

Wedzony, K.; Mackowiak, M.; Fijał, K. and Gołembiowska, K. (1996). Ipsapirone enhances the dopamine outflow via 5-moemoeceptors in the rat prefrontal cortex. Eur. J. Pharmacol.,305(1–3):73–78.

Wilkerson, A. and Levin, E.D. (1999). Ventral hippocampal dopamine D1 and D2 systems and spatial working memory in rats. Neuroscience, 89(3):743-749.

Yashpal, K. and Henry, J.L. (1984). Substance P anatogue blocks sp-induced facilitation of a spinal nociceptive reflex. Brain Res. Bull.,13(4): 597-600.

Zhang, J.; Chen, L. and Sun, J. (2018). Oxoisoaporphine Alkaloids: Prospective Anti-Alzheimer's Disease, Anticancer, and Antidepressant Agents. Chem. Med. Chem., 13:1262-1274.

Zhang, Y.C.; Zhu, X.Q. and Zhang, X.H. (2017). Effect of methylphenidate on c-Fos expression in parvalbumin interneurons of juvenile rat frontal cortex. Sheng Li Xue Bao., 69(4):378-384.

Zhu, X.H.; Qiao, H.; Du, F.; Xiong, Q.; Liu, X.; Zhang, X.; Ugurbil, K. and Chen, W. (2012). Quantitative imaging of energy expenditure in human brain. Neuroimage, 60: 2107–2117.

نبات القراص يحسن وظائف المخ في نموذج الجرذان المشابه للتوحد المحدث بحمض البروبيونيك خلال الامينات الاحادية وحاملات الطاقة

الهام حسن احمد علي[1] ، محمد كامل حسن[2] ، اسامة احمد عباس[2] ، هبة ايهاب الملاحي[2] ، علي حسين ابو المعاطي[2]

1 - قسم علم الحيوان – كلية البنات للاداب والعلوم والتربية- جامعة عين شمس

2 - قسم علم الحيوان -كلية العلوم – جامعة بور سعيد

المستخلص

تهدف هذه الدراسة الى معرفة تأثير نبات القراص (الاوراق والجذور) كلا علي حده علي التغير في السلوك والامينات الاحادية وحاملات الطاقة فى نموذج الجرذان المشابه للتوحد المحدث بحمض البروبيونيك ومقارنته بعقار الرسبريدون. تم تقسيم ستين جرذا الي خمس مجموعات متساوية (ن= 12) وعولجت لمدة 17 يوما علي النحو التالي: 1- المجموعة الضابطة تلقت محلول ملحي (PBS- ك 1ملي / كجم بالغشا ء البريتوني) +(0.5 جرام/ 100 ملي-ك 5 ملي / كجم من وزن الجسم عن طريق الفم) من الميثيل كربوكسي سليلوز (CMC) ، 2 – المجموعة المعاملة بحمض البروبيونيك عوملت (250 ملجم / كجم ك 1 مل / كجم من وزن الجسم بالغشاء البريتوني) +CMC ، 3-المجموعة المعاملة بالبروبيونيك + الرسبريدون (1 ملجم / كجم من وزن الجسم عن طريق الفم) ، 4- المجموعة المعاملة بالبروبيونيك + اوراق نبات القراص (50 ملجم / كجم من وزن الجسم عن طريق الفم) و 5- المجموعة المعاملة بالبروبيونيك + جذور نبات القراص (50 ملجم / كجم من وزن الجسم عن طريق الفم). تم إجراء اختبار الغرف الثلاثية والمتاهة Y من اليوم 15 إلى 17. ثم تم التضحية بالجرذان في اليوم الثامن عشر ، واستُخدمت أنسجة القشرة المخية وقرن امون والمخ المتوسط لتقدير محتويات الدوبامين ، النورإبينيفرين والسيروتونين جنبًا إلى جنب مع حاملات الطاقة (ATP، ADP و AMP). وأظهرت النتائج أن مستخلص جذور القراص يمكن أن تحسن في السلوك مع تحسين نظام الأمينات الاحادية والطاقة الحيوية. في المقابل ، كان لمستخلصات اوراق القراص تأثير ضعيف على التحسن السلوكي ومستويات الأمينات الاحادية والطاقة الحيوية. لذلك ، يمكن أن نخلص إلى أن مستخلص جذور القراص كان له تأثير وقائي بسبب تأثيره على النظم السلوكية والأمينات الاحادية وحاملات الطاقة